

A Theory for Myogenic and Metabolic Control
of Vascular Resistance in Skeletal Muscle
during Autoregulation of Blood Flow

By
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Lund 1984



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This summary is based on the following publications:

I. BORGSTRÖM, P., GRÄNDE, P.-O. & LINDBOM, L. 1981. Responses of single arterioles in vivo in cat skeletal muscle to change in arterial pressure applied at different rates. *Acta Physiol Scand* 113:207-212.

II. BORGSTRÖM, P. & GRÄNDE, P.-O. 1979. Myogenic microvascular responses to change of transmural pressure. A mathematical approach. *Acta Physiol Scand* 106:411-423.

III. BORGSTRÖM, P., GRÄNDE, P.-O. & MELLANDER, S. 1982. A mathematical description of the myogenic response in the microcirculation. *Acta Physiol Scand* 116:363-376.

IV. BORGSTRÖM, P., GRÄNDE, P.-O. & MELLANDER, S. 1984. An evaluation of the metabolic interaction with myogenic vascular reactivity during blood flow autoregulation. *Acta Physiol Scand* 122:275-284.

V. GESTRELIUS, S. & BORGSTRÖM, P. 1985. A dynamic model of smooth muscle contraction. In manuscript.

VI. BORGSTRÖM, P. & GESTRELIUS, S. 1985. Integrated myogenic and metabolic control of vascular tone in skeletal muscle during autoregulation of blood flow. In manuscript.

In the text, these papers are referred to by their Roman numerals.

INTRODUCTION

The control of the peripheral circulation comprises several regulatory mechanisms which, via integrated actions on the vascular resistance, exchange, and capacitance functions serve to satisfy nutritional and other local demands of the tissues and to govern overall cardiovascular homeostasis. Two main principles in peripheral circulatory control may be distinguished. Firstly, the remote (central) control systems which, via different vasomotor fibre systems and blood-borne vasoactive factors, are responsible mainly for overall cardiovascular homeostasis. Secondly, the local (intrinsic) control systems which, via regulatory mechanisms originating from sites within the tissue itself, appear to subserve vitally important nutritive and protective circulatory functions for the tissues proper. The present studies deal with local vascular control and, more specifically, with the organization of myogenic and metabolic regulatory mechanisms and their complex mutual interactions in various local circulatory adjustments, such as autoregulation of blood flow.

Previous concepts of local myogenic and metabolic vascular control

The myogenic hypothesis originates from the classical work by Bayliss in 1902 in which he postulated that the intravascular blood pressure, via distension, caused a direct stimulating action on the vascular smooth muscle and enhanced contractility, contributing to vascular tone and its regulation. His hypothesis was based on a series of careful, though not entirely unequivocal, experiments and on analogies to the responses of other types of smooth muscle exposed to stretch. Bayliss clearly envisaged the intravascular pressure as a continuing stimulus to the vascular smooth muscle, though without direct evidence. The myogenic hypothesis, however, became seriously questioned for a number of decades, starting with a critical study by Anrep (1912) who claimed that Bayliss' experimental results could be explained on the basis of local metabolic mechanisms. The view was then held for considerable length of time that change of tissue metabolite concentration was the essential local factor that regulated vascular tone.

The myogenic concept was, however, revived by the results of later hemodynamic studies, starting with Folkow's work in 1949. He could quite convincingly demonstrate active myogenic reactions to changes in blood pressure under circumstances with seemingly negligible metabolic

influence. His studies led to a great many other investigations of myogenic reactivity, especially of the phenomenon of autoregulation of blood flow, leading with time to the compromise view (Folkow 1962, 1964, Johnson 1964) that myogenic as well as metabolic mechanisms are synergistically responsible for that particular reaction.

In later more detailed studies it was shown that a very effective myogenic/metabolic autoregulation of capillary hydrostatic pressure existed over a wide range of arterial pressures, effected via changes of pre-/postcapillary resistances, and serving to maintain the normal transcapillary Starling fluid equilibrium during arterial hypo- and hypertension (Järhult & Mellander 1974). Further, increased hydrostatic load on the vascular bed was shown to cause an especially marked myogenic constriction of the precapillary sphincters which, via decreased functional capillary surface area established an 'autoregulating transcapillary filtration' during increased transmural pressure, hence preventing the expected gross oedema formation (Mellander, Öberg & Odelram 1964). Of special interest in this context was the fact that these whole-organ studies strongly pointed to the idea that the arterial microvessels were especially sensitive to myogenic stimuli. This view was confirmed by detailed vital microscopy observations in the microcirculation, for instance by Johnson and collaborators (e.g. 1968, 1976, 1980) and by Baez et al. (1974), which demonstrated that increased vascular transmural pressure indeed caused the predicted myogenic diameter changes of arterioles and precapillary sphincters. Johnson and Wayland (1967) also demonstrated distinct dependence of capillary flow periodicity upon change of intravascular pressure.

Although all these studies provided strong support for the myogenic hypothesis, the receptor mechanism of the myogenic response has been largely a matter of speculation. There are, however, two basic theories that have been proposed for the mechanisms underlying the myogenic reactions in vascular smooth muscle. In the first of these, the myogenic response is thought to be caused by a stretch-receptor inserted in parallel with the vascular smooth muscles and sensitive to changes in muscle length. This mechanism has been criticized on the ground that it is self-limiting since a muscle shortening in response to raised distending pressure automatically would abolish the primary receptor stimulus (cf. Guyton 1964). Hence, this theory is not compatible with the

reaction pattern as observed during autoregulation of blood flow in vivo where the vascular smooth muscles respond with a reduced length at a rise in perfusion pressure. An interesting hypothesis for how this problem might be circumvented in the in vivo operation of the myogenic control system was presented by Folkow (1964). The second theory, which has been proposed by several investigators (e.g. Johnson 1974, Johnson & Wayland 1967, Koch 1964, Thurau 1964), is based on the assumption that vascular wall tension is the controlled variable in the myogenic control. A shortcoming of this latter theory, in which the myogenic sensor element is thought to be coupled in series with the vascular smooth muscles, is that a well controlled wall tension implies a high gain in the feedback, which would make blood flow decrease at a rise in perfusion pressure (cf. Thurau 1964, Navar et al. 1974). Hence, only with a sufficiently low gain, implying a poorly controlled wall tension, blood flow would be maintained constant (autoregulated) as perfusion pressure is increased (cf. Johnson & Intaglietta 1976). The hypothesis that wall tension is an important variable has obtained experimental support by, for instance, Burrows and Johnson (1979) and Bouskela and Wiederhielm (1979) who showed that wall tension calculated from in vivo measurements of intravascular pressure and arteriolar diameters tended to be maintained as pressure was changed, although a substantial error signal was evident, indicating a low gain in the myogenic feedback. The fact that there is a substantial error signal implies that wall tension is not perfectly controlled, although it still might be an important variable in the myogenic control, serving as a trigger for the myogenic sensor.

Another problem has been the lack of detailed knowledge about the cellular mechanisms of the myogenic control. This problem has, however, been partly clarified in later studies. For instance, a study of electrical and mechanical activity in the rat portal vein in vitro demonstrated that myogenic excitatory and inhibitory responses can be attributed to facilitation and inhibition of spike discharge primarily generated from local 'pacemaker' cells (Johansson & Mellander 1975). This study, and later ones obtained from whole-organ observations on microvessels in vivo (Grände, Lundvall & Mellander 1977, Grände & Mellander 1978), further demonstrated the existence of a prominent dynamic, or rate-sensitive, component in myogenic vascular control, in addition to the previously known static component.



Intense research has also been devoted to the local metabolic control system. Such investigations have mainly been focused on the problem to identify the metabolic factors responsible for local metabolic control but have so far hardly helped to reveal the exact mode of operation of this control system. Thus extensive investigations by Berne's group (e.g. Imai, Riley & Berne 1964, Rubio & Berne 1969) have presented ample evidence for the view that adenosine is an important metabolic regulator of vascular tone, at least in the myocardium. In skeletal muscle, on the other hand, several factors seem to contribute to the metabolic vascular control, such as tissue hypoxia, tissue hyperosmolarity, and increased concentrations of potassium, adenosine and inorganic phosphate (for ref. see Mellander & Johansson 1968, Johnson 1978, Sparks 1980). Guyton and co-workers (Fairchild et al. 1966, Carrier et al. 1964, Guyton et al. 1964) suggested that oxygen might act directly on the vascular smooth muscle cells thereby initiating vascular tone, whereas Duling (1972) proposed that oxygen just acted to support the muscle contractions and that the effect of hypoxia was indirect via release of dilator factors from the parenchymal cells.

For a description of vascular regulation we need to know the true nature of the all-important so called intrinsic, 'basal vascular tone', a term which denotes the marked contractile state of the vascular smooth muscle that persists in most precapillary vessels after complete elimination of all known extrinsic excitatory influences. All vascular regulatory mechanisms seem to operate upon this basal vascular tone by evoking superimposed excitatory or inhibitory reactions. Very few studies have, however, dealt specifically with the mechanisms underlying basal vascular tone. Yet, the mechanisms which create this tone might be considered to dominate normal vascular regulation, whereas the superimposed control systems act more as modulators, though powerful ones. Various tentative explanations for this basal tone have been proposed in the literature. Mention was made above that oxygen could act directly on the vascular smooth muscle and thereby cause the normal contractile state. Further, it has been postulated (Johansson & Bohr 1966) that there is a humoral plasma factor which is responsible for the tonic activity in the small blood vessels, but the evidence is so far incomplete and the nature of the factor is still unknown. It has also been envisaged by several researchers that basal tone is coupled in some way to the myogenic vascular response (Bayliss 1902, Folkow 1949, Löfving & Mellander 1956,

Folkow 1962, 1964). This myogenic concept recently received more direct experimental support (Mellander & Arvidsson 1974, Lalone 1975, Grände, Borgström & Mellander 1979) which indicated that the initiation and maintenance of normal basal tone in the arterial vessels seem to be intimately related to the arterial blood pressure, exerting a 'tonic' excitatory influence on the vascular smooth muscle.

Aim of the present investigations

The studies in this paper deal with the local control of vascular resistance in cat skeletal muscle. In particular, they are concerned with the mode of operation of the myogenic regulatory system and to what extent myogenic reactions are modulated by metabolic vasodilator factors in integrated intrinsic vascular control.

In previous studies from our laboratory (Grände et al. 1977, Grände & Mellander 1978), myogenic mechanisms in the sympathectomized vascular bed of cat skeletal muscle were studied in detail with a whole-organ technique which permitted, with an indirect approach, a separation between segmental resistance responses in 'proximal arterial vessels', 'microvessels', and 'large veins'. Those studies revealed a moderate static component in the myogenic response to change of overall vascular transmural pressure in both the proximal arterial vessels and the microvessels and a much more prominent dynamic component confined mainly to the microvessels. In Paper I of this series of investigations the validity of this whole-organ technique for description and separation of segmental myogenic vascular reactions was tested with a more direct approach, viz. by direct vital microscopic observations of the reactivity of single arterioles. This study revealed that the basic myogenic reaction pattern observed with the whole-organ technique in terms of a rate-sensitive, dynamic as well as a static component in the myogenic control indeed could be demonstrated directly on single arterioles. The dynamic responses were thus shown to be confined to arterioles smaller than about 20 μm while the steady state responses were present also in larger arterioles. Such similarity seems to justify the use of the whole-organ technique for the study of various locally controlled vascular reactions in the further analyses performed in this series of investigations.

The local myogenic and metabolic vascular control systems operate via

complex interacting feedback loops whose exact events are difficult to predict directly from in vivo observations. A mathematical model analysis, based on sound physiological concepts, may for reasons discussed in greater detail below (Methodological considerations) be of great help to better understand the regulatory mechanisms and their underlying physiological events in the sometimes quite puzzling vascular adjustments observed in vivo. In Paper II, a mathematical model was designed which permitted simulations of our previously demonstrated dynamic and static myogenic microvascular resistance responses in vivo to changes in vascular transmural pressure. The model was based on a force equilibrium in the microvessel wall and it permitted tests of the hypothesis that myogenic reactions are triggered by and related to change of wall tension. In Paper III, this mathematical model was refined so as to also include the myogenic reactions of the 'proximal arterial vessels' and it, further, took into account the effects of delay in the biological receptor-effector chain and of shifts along the length-force curve of the vascular smooth muscle, which improved the applicability of the model. In Paper IV, an attempt was made to evaluate by an in vivo approach the possible metabolic interaction with myogenic vascular reactivity during autoregulation of blood flow. The interpretation of the results of those experiments was greatly facilitated by the use of the model designed in Paper III and suggested a significant blood flow dependent metabolic interaction with myogenic reactivity even at such minute flow changes that occur in the autoregulatory pressure range. In Paper V, a mathematical model for the smooth muscle contractile machinery was designed in an attempt to better define the basic effector unit in vascular control. This muscle model was included in a further refined mathematical model presented in Paper VI which in more detail described the myogenic and metabolic feedback control of vascular resistance in skeletal muscle. The blood flow dependent metabolic interaction with myogenic reactivity, described in Paper IV, was also included in this final model and with such characteristics it was found capable of simulating faithfully the vascular reactions to a variety of experimental interventions accomplished by change of transmural, arterial, as well as venous pressures. This model can therefore serve as a comprehensive theory for the mechanisms underlying the vascular reactions in autoregulation of blood flow.

METHODOLOGICAL CONSIDERATIONS

MATHEMATICAL MODEL ANALYSIS

The role of mathematical modeling. In the analysis of such complex regulatory mechanisms as involved in the local vascular control, mathematical modeling can be a useful, sometimes almost indispensable, tool. The process of making predictions based on complex theories is difficult. By formulating the theory as a system of mathematical equations we need not rely on intuition to make the predictions. Fig. 1, reproduced from Phair (1982), describes how mathematical models are used in the analysis of biological phenomena. When investigating a system, a hypothesis is often postulated with the purpose of describing or explaining the mechanisms underlying the experimental observations. Mathematical modeling is the process by which such hypotheses are formulated and tested. The comparison between the model predictions and the experimental observations, represented by the diamond in Fig. 1, can result in either a match or an inconsistency. The latter corresponds to an inadequately postulated hypothesis which then can be rejected. Such inconsistency can thus serve as a guide and incitement for a reformulation of the theory which, in turn, again is tested. Modeling can thus increase the rejection rate of erroneously formulated theories. A match, on the other hand, corresponds to experimental corroboration of the postulated theory thus supporting the hypothesis. Confidence in models derives from the ability to match simultaneously the constraints imposed by a wide variety of experimental observations. A first power in modeling is thus the ability to predict with precision the consequences of complex theories, mostly leading to reformulation of postulated hypotheses. A second important capability provided by modeling is estimation of physiological parameters that are not directly measurable with available experimental techniques, an option which can be of great importance for better understanding of the mechanisms behind the observed phenomena. The derived model does also represent a summary of the current theory wherefore models can be looked upon both as goal and means in the analysis of a biological system.

The main advantage of the model designed in Paper II was thus the power of predicting the hemodynamic consequences of proposed vascular wall tension related myogenic mechanisms. The complicating effects of Laplace's and Poiseuille's laws, and wall/lumen variations on wall

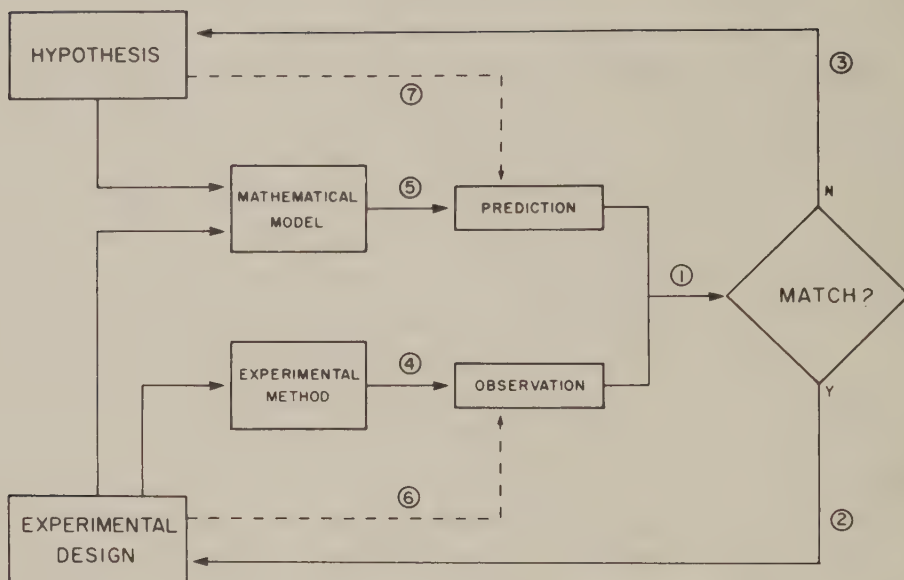


Fig. 1. Block scheme illustrating the role of mathematical modeling in the analysis of a physiological system. (1) The comparison of model predictions and experimental observations. (2) Experimental corroboration. (3) Rejection and modification of the hypothesis (although there are times when the experimental data must be questioned). (4) Experimental techniques giving biological observations. (5) Simulation of the experiment using a dynamic mathematical description of the hypothesis to be tested. This permits prediction with precision. (6) The process, described in the 16th century, of collecting data by intuition without recourse to experiments. (7) For hypotheses consisting of three or more interacting variables, the process represented should be equally suspect.

tension etc. make it very difficult to interpret directly the observed vascular resistance responses. The model designed in Paper II was also used to estimate changes in wall tension and vessel radius and these estimations suggested that wall tension was not the controlled variable in myogenic vascular regulation. The refined model designed in Paper III which, like the first version, simulated purely myogenic mechanisms was used in Paper IV to predict the effects of physical factors inherent in altered basal vascular tone and intravascular pressure on the magnitude of a vascular resistance response to a given transmural pressure stimulus.

The main purpose of the final mathematical model in this series of investigations (Paper VI), designed for description of integrated myogenic and metabolic control of vascular resistance, was to test the

hypothesis that myogenic wall tension (force) related myogenic mechanisms are constantly modulated by blood flow dependent metabolic factors during autoregulation of blood flow. This model, in addition, had the great advantage of being interpretable on the cellular (smooth muscle) level which further increased its usefulness in the analysis.

Computational methods. The mathematical model designed in Paper II was solved on a CAI Alpha LSI 2/20B computer using the Runge-Kutta method for handling the differential equation.

The models designed in Papers III, V and VI were solved on a CAI Alpha LSI 4/90 computer which has an accuracy of slightly more than 7 digits, using a revised single precision version of a program for numerical integration of partitioned stiff ordinary differential equations and differential algebraic systems developed by Söderlind (1980).

EXPERIMENTAL METHODS FOR BIOLOGICAL OBSERVATIONS

Detailed descriptions of the methods employed in the series of whole organ experiments in Papers IV and VI as well as for the experiments performed on single arterioles in Paper I were given in the original papers. Below follows only a brief summary of the principal methodological arrangements.

Whole-organ technique. The experiments were performed on cats of both sexes (bwt 2.9 - 4.9 kg) anaesthetized i.v. with urethane (100 mg x kg bwt⁻¹) and α -chloralose (50 mg x kg bwt⁻¹). Observations were made on the acutely sympathectomized lower leg muscles of the hindlimb which was separated from the body except for its main vascular connections, the popliteal artery and vein. The muscle region to be studied was enclosed in a plethysmograph, the hydrostatic pressure in which could be varied permitting applications of overall vascular transmural pressure changes. Venous outflow pressure could be altered by means of adjusting the level of the orifice of the venous outflow tubing. Also the arterial inflow pressure could be changed to desired levels below the systemic pressure by means of a screw clamp on the arterial inflow tubing. Mean arterial blood flow (Q) to the region was recorded with a pressure gradient flowmeter (Grände & Borgström 1978). Arterial inflow pressure (P_A) and venous outflow pressure (P_V) to the region were recorded with Statham transducers (P23-ID) as was also done in some experiments with the

pressure from arterial microvessels (P_{SA}) and from venous microvessels (P_{SV}).

Total vascular resistance defined as $(P_A - P_V)/Q$ and the regional resistances: 'proximal arterial' resistance defined as $(P_A - P_{SA})/Q$, and 'microvascular' resistance defined as $(P_{SA} - P_{SV})/Q$ were obtained by means of differential pressure transducers and analogue divider circuits.

Experiments on single arterioles. The microscopic observations (Lentz intravital microscope) were made on the α - and β -adrenergically and cholinergically blocked vascular bed of the acutely sympathectomized left tenuissimus muscle of cat which was prepared as described previously (Lindbom, Tuma & Arfors 1980). The tenuissimus muscle was perfused with a servo-controlled roller pump (Borgström, Clementz & Grände 1981) via a shunt circuit inserted between the abdominal aorta and the left iliac artery. The pump delivered a pulsatile arterial pressure, the level of which could be adjusted to desired levels. Throughout the surgical and experimental procedures the tenuissimus muscle was kept moist by a Krebs-Henschel solution of 36° C which was bubbled with a gas-mix of N_2 and C_{O_2} giving physiological values of P_{O_2} (10-30 mmHg), P_{CO_2} (40 mmHg) and pH (7.4) in the perfusion environment of the exposed muscle.

Drugs. Blood coagulation was prevented by i.v. administration of heparin (1000 IU x kg bwt⁻¹), platelet aggregation was minimized by i.v. administration of piroxicam (5 mg x kg bwt⁻¹) in the whole-organ experiments and of indometacin (1 mg x kg tissue⁻¹ every 30 min) in the experiments on single arterioles. Regional β -adrenergic blockade was accomplished by close arterial administration of propranolol chloride (1 mg x kg tissue⁻¹). Regional α -adrenergic and cholinergic blockade was in the experiments with graded light exercise in Paper IV accomplished by close arterial administration of phenoxybenzamine hydrochloride (10 mg x kg tissue⁻¹) and atropine sulphate (1 mg x kg tissue⁻¹). Papaverine (100 mg x kg tissue⁻¹ i.a.) was used to abolish vascular tone.

RESULTS AND COMMENTS

1. Static and dynamic myogenic reactivity demonstrated on single arterioles in vivo in cat skeletal muscle (Paper I).

The reaction pattern of the vascular bed of cat skeletal muscle to changes in vascular transmural pressure has been studied previously in detail with a whole-organ technique (Grände et al. 1977, Grände & Mellander 1978) permitting, indirectly, a separation of responses evoked in 'proximal arterial vessels' (i.d. $>$ about 20 μm) and in arterial 'microvessels' (i.d. $<$ about 20 μm). Those studies revealed a dynamic rate-sensitive component in the myogenic response in addition to the previously known static one. The dynamic myogenic component observed with this indirect whole-organ technique was suggested to be mainly confined to the 'arterial microvessels', whereas the 'proximal arterial vessels' merely exhibited a static myogenic response.

The experiments performed in Paper I served to test if the described differentiated myogenic pattern of response in the arterial vessel segments observed indirectly with the whole organ technique could be verified with a more direct experimental approach. For this purpose a vital microscopic technique was used in an attempt to analyze corresponding myogenic reactions directly on single arterioles of various dimensions in skeletal muscle. These observations, for methodological reasons, were made during standardized increases/decreases in arterial inflow pressure and not during changes in overall vascular transmural pressure. Despite the fact that change of arterial pressure, in contrast to change of overall transmural pressure, involves a primary blood flow change and, hence, a metabolic stimulus, in addition to the myogenic stimulus, the directly observed dynamic myogenic responses in the small arterioles ($<20 \mu\text{m}$) quite closely resembled the myogenic microvascular reactions observed in vivo with the above mentioned whole-organ technique. Fig. 2 illustrates original recordings of diameter variations in a small ($\sim 15 \mu\text{m}$) arteriole during a given increase and decrease in arterial perfusion pressure applied at a high rate (panel A) and a low rate (panel B). It can be seen that the fast, but not the slow, phasic pressure change evoked pronounced dynamic myogenic constrictor and dilator responses in the arteriole. The steady state (static) constrictor response evoked during constant increased pressure was comparatively small and, as expected, of about the same magnitude in both experiments

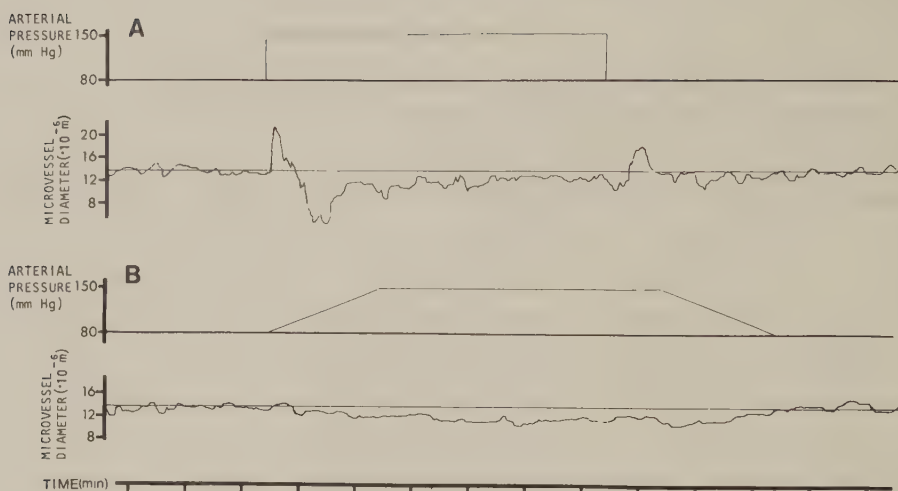


Fig. 2. Original vital microscopy registrations of diameter changes of an arteriole ($\approx 15 \mu\text{m}$, i.d.) in skeletal muscle in response to an arterial pressure increase and decrease applied at a high (panel A) and a low rate (panel B). The reaction pattern observed with this direct vital microscopic technique was much the same as that obtained in arterial microvessels $< 20 \mu\text{m}$ with the whole-organ technique (see Fig. 3) insofar as a fast pressure increase/decrease caused a prominent dynamic constrictor/dilator response and a relatively small static response in the steady state of increased pressure; pressure increase at low rate only elicited the static response.

(panels A and B). This study further showed that large-bore arterioles ($> 35 \mu\text{m}$) only exhibited a static, but virtually no dynamic, myogenic response to change of arterial pressure. These direct observations thus showed a very similar differentiated myogenic reaction pattern in large-bore and fine-bore arterial vessels to that described with the whole-organ technique. This study thus seems to justify the use of observations with the whole-organ technique for experimental corroboration of the mathematical model predictions made in the following studies.

2. Mathematical analysis of myogenic microvascular responses to change of transmural pressure (Papers II and III).

As mentioned above myogenic responses of sympathectomized cat skeletal muscle to changes in vascular transmural pressure have been investigated previously with a whole-organ technique (Grände et al. 1977, Grände & Mellander 1978). In those experiments all parts of the vascular bed were exposed to change of vascular transmural pressure (P_T) applied at various rates. The P_T change was accomplished by varying the extravascular pressure with a plethysmographic technique. This procedure made it

possible to avoid simultaneous changes in the perfusion pressure in order to minimize a blood flow dependent, direct metabolic interference with myogenic mechanisms. These studies revealed a dynamic or rate-sensitive component in the myogenic response of the arterial microvessels (i.d. < about 20 μ m), graded in relation to the rate of the dynamic transmural pressure change and a more moderate static response during constant increased P_T (see Fig. 3, panel B).

These static and dynamic myogenic microvascular reactions were in Paper II postulated to be evoked by a myogenic receptor mechanism triggered by and related to vascular wall tension and its rate of change. The myogenic vascular control system involves complex feedback mechanisms and non-linear biophysical factors which make direct interpretation of in vivo observations, such as those shown in Fig. 3, quite difficult. To be able to better predict the hemodynamic consequences of the hypothesis of wall tension related, rate-sensitive myogenic responses, a mathematical model for description of myogenic microvascular responses to a change of P_T was designed (Paper II). The vascular bed, in analogy to the biological analysis, was in this model represented by three series-coupled sections: Firstly, the 'proximal arterial section', represented by a number of parallel-coupled cylindrical tubes with the same resistance as arterial vessels > 20 μ m (i.d.; see Grände 1979), defined in vivo by the arterial inflow pressure (P_A) and the small artery pressure (P_{SA}). Secondly, the 'microvascular section' was represented by a number of parallel-coupled tubes with the same resistance as arterial vessels < 20 μ m (i.d.), defined in vivo by P_{SA} and small vein pressure, P_{SV} . Thirdly, the 'large vein section', represented by a number of parallel-coupled tubes with the same resistance as venous vessels in vivo defined by P_{SV} and the venous outflow pressure, P_V .

The model was based on a force equilibrium in the microvessel wall, including the following passive forces: A force related to transmural pressure (Laplace's law), an elastic force, and a force related to wall viscosity. Further, it included the postulated active myogenic static and dynamic forces as well as an active force related to basal vascular tone.

The following assumptions were made:

- a) Dynamic myogenic reactivity was confined to the arterial microvessels smaller than about $20\ \mu\text{m}$ (i.d.) (cf. Grände et al. 1977, Grände & Mellander 1978).
- b) The evoked myogenic responses were directly proportional to wall tension and its rate of change (hypothesis to be tested).
- c) Blood flow in these vessels was assumed to obey the law of Poiseuille and, hence, their vascular resistance was assumed to be inversely proportional to the forth power of the vessel inner radius.
- d) The elastic properties of the microvessel wall were considered to be linear.
- e) Microvessel wall viscosity was set proportional to the rate of change of vessel radius.
- f) The more proximal arterial vessels (i.d. $>20\ \mu\text{m}$) were treated as rigid tubes with constant vascular resistance (cf. Grände et al. 1977).
- g) Microvascular outflow pressure (small vein pressure) was considered constant (cf. Grände et al. 1977).

This model for description of microvascular myogenic resistance responses to change of transmural pressure was tested for a variety of transmural pressure ramp stimuli and found capable of predicting essential characteristics of the vascular responses observed in vivo. Fig. 3 (panels B and C), shows an example of such a comparison. Panel B shows for one representative experiment how microvascular resistance in skeletal muscle in vivo was influenced by a given total increase in P_T of 30 mmHg applied at 3 different rates (dP_T/dt : 0.63, 1.25, and 3.75 mmHg) and by a subsequent decrease in P_T back to the control level at the same given rates. These tracings demonstrate pronounced dynamic constrictor and dilator responses during the period of changing P_T , graded in relation to dP_T/dt both for positive and negative values. They also show the comparatively small static constrictor response in the steady state period of constant increased P_T . Fig. 3, panel C, illustrates corresponding microvascular resistance responses obtained with the described mathematical model. It can be seen that the biological and the predicted resistance curves showed resemblance as regards their fundamental characteristics. Thus, the amplitudes of the dynamic constrictor and dilator responses and the amplitude of the static constrictor response were quite similar and this also applied to the

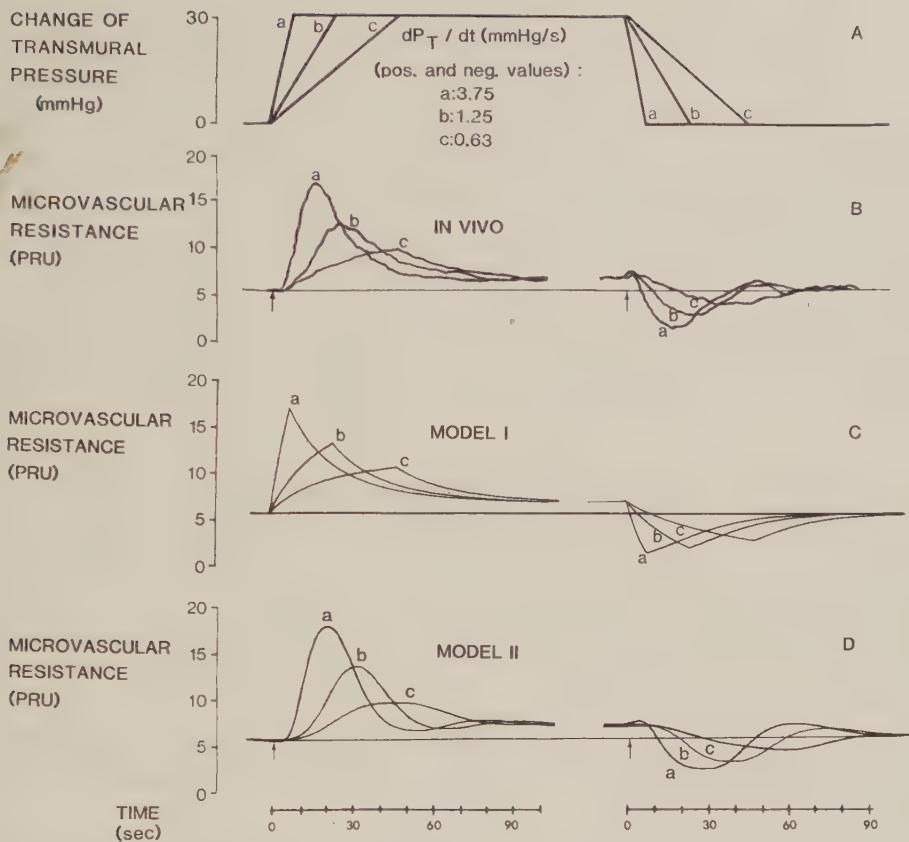


Fig. 3. Myogenic microvascular resistance responses in sympathectomized cat skeletal muscle (panel B) evoked by increase and subsequent decrease in vascular transmural pressure, (P_T), by 30 mmHg applied at three different rates (panel A) compared to predictions of corresponding responses by the model presented in Paper II (panel C) and by the refined model presented in Paper III (panel D). Both models were capable of predicting the general basic pattern of response observed in vivo (panel B) in terms of pronounced dynamic constrictions and dilatations, graded in relation to the rate of the pressure change, and a relatively small static constriction in the steady state of constant increased pressure. The best predictions were, however, obtained with the refined model (panel D) which adequately simulated also the smoothness of the resistance curves at the onset and offset of the dynamic transmural pressure stimuli as well as the initial delay and other time characteristics of corresponding in vivo curves.

general configuration of the curves, except that at the onset and offset of the dP_T/dt stimulus. The good matching between model predictions and in vivo observations strengthened the myogenic hypothesis in general and, in addition, corroborated the hypothesis that myogenic reactions are related to wall tension and its rate of change.

The fact that these simulated resistance responses, in contrast to the biological ones, started momentarily and ceased abruptly upon onset and

offset of the dP_T/dt stimulus could be ascribed to the negligence in this first model version of certain biological characteristics, viz. time delay and general slowness of the in vivo receptor-effector system and the effects of an apparently existing dynamic myogenic 'pacemaker' spike afterdischarge (cf. Johansson & Mellander 1975). Further, the disregard of shifts along the length-active force curve for the vascular smooth muscle and also of microcirculatory effects from the proximal series-coupled arterial vessels and the large veins (which via overall flow alterations have considerable influence on mean distending pressure in the microvessels), limited the more general applicability of this first model.

The factors mentioned in the foregoing paragraph were incorporated in a second mathematical model designed in Paper III. This mathematical model was a refined version of the one just described but it took into account also the following:

- a) A linear length-active force relationship was assumed (cf. Johansson 1975, Mulvany & Warshaw 1979).
- b) Pressure induced myogenic reactions in the 'proximal arterial vessels' were incorporated and treated mathematically as described for the microvessels (Paper II).
- c) Biological 'delay' was taken into account by describing this factor in the links between wall tension change and the resulting active myogenic forces in terms of a second order differential equation.
- d) Passive vessel wall viscosity was assumed to decrease with increasing rate of wall movement (cf. Bergel 1960).
- e) The effect of large vein resistance on microvascular pressure was taken into account by letting small vein pressure (P_{SV}) be a linear function of P_T (cf. Grände et al. 1977).

When these additional factors were incorporated, the matching between model predictions and corresponding in vivo observations was much improved as was also the applicability of the model. Fig. 3, panel D, illustrates the ability of this refined model to simulate corresponding microvascular myogenic resistance responses in vivo (panel B). It can be seen that this model was clearly superior to our previous one, insofar as it described more faithfully the general time characteristics of the biological resistance curves, including the normal smoothness in their configurations, the damped oscillatory behaviour, etc.

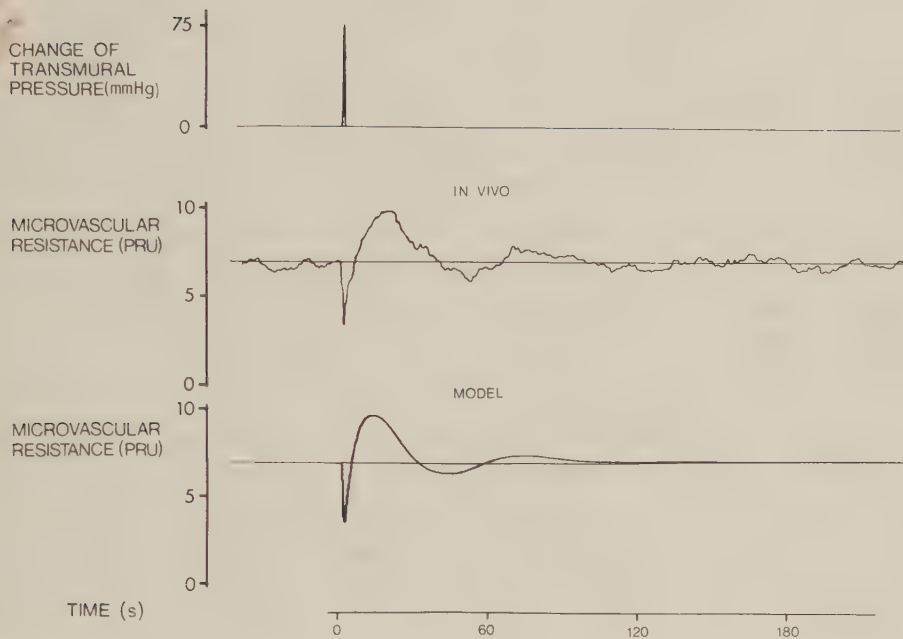


Fig. 4. Microvascular resistance response to an impulse vascular transmural pressure stimulus (amplitude 75 mmHg, duration 1.5 ms) as observed in vivo (middle panel) and as predicted with the model (lower panel). Note that both curves show the same pattern of response, an initial resistance decline followed by an active myogenic constrictor response, fading away with oscillations around control resistance.

Fig. 4 shows that this model in addition was able to simulate myogenic reactions in response to a quick transient change of transmural pressure ('impulse stimulus'). The in vivo response (middle panel) was evoked by a transmural pressure impulse stimulus with a duration of 1.5 s and an amplitude of 75 mmHg. It can be seen that after an initial transient resistance decrease, the impulse stimulus led to a very quick active dynamic myogenic constriction which gradually faded away with oscillations around control resistance. Basically the same pattern of response was obtained with the model (lower panel). Such ability of the model to simulate the in vivo myogenic responses to impulse, as well as ramp, transmural pressure stimuli increased its usefulness as a tool for elucidating complex biological problems, practical examples of which were illustrated in Paper III (Fig. 6) and in section 3 of Results below.

3. Experimental evaluation of the metabolic interaction with myogenic reactivity in the local vascular control of skeletal muscle (Paper IV).

The investigations described in section 2 of Results were concerned only with myogenic mechanisms in local vascular control. However, vascular reactions underlying such important phenomena as autoregulation of blood flow are most likely accomplished by an interaction of myogenic and metabolic regulatory mechanisms (e.g. Folkow & Neil 1971, Johnson 1980). There is, however, relatively little direct experimental proof of such an interaction, and basic information about postulated feedback in local vascular control is therefore still lacking. In this study an attempt was made to evaluate the possible metabolic influence during blood flow autoregulation. This was done by analyzing to what extent a purely myogenic constrictor response to a standardized vascular transmural pressure impulse stimulus was altered when evoked at different steady state blood flow levels accomplished by graded change of arterial blood pressure. The applied transmural pressure impulse, produced by change of extravascular pressure, was of such short a duration (<2 s) that the test stimulus and the ensuing active dynamic myogenic constrictor response *per se* could be considered to cause negligible interference with the metabolic vascular control system.

The analysis of the myogenic response to a pressure impulse stimulus is, however, complicated by the fact that, like any other vascular response, its amplitude is also influenced by the level of vascular tone prevailing at the time the test stimulus is applied (Grände 1979), and a change of vascular tone does underly the reaction of autoregulation of blood flow. Physical factors inherent in the effects of, for example, the laws of Laplace and Poiseuille as well as the vascular smooth muscle length-active force relationship are responsible for such dependency (cf. Borgström & Grände 1980, Paper III, Fig. 6). It follows that such factors, as well as the vascular wall tension change evoked by altered arterial pressure, had to be taken into consideration in the interpretation of the present *in vivo* results. This was done with the aid of the mathematical model designed in Paper III which incorporated such effects.

Fig. 5 (upper panel, solid curve) shows average data for the peak amplitude of the myogenic constrictor response to the standardized pressure impulse, applied at different steady state mean arterial

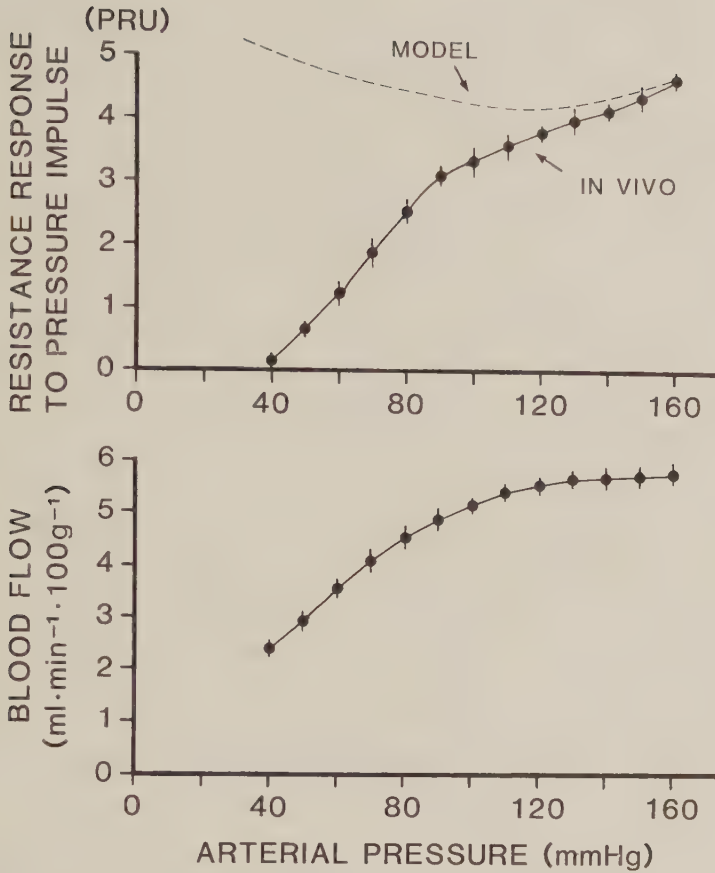


Fig. 5. Upper panel: The solid curve depicts average data for the amplitude of the in vivo vascular myogenic constrictor response to a standardized transmural pressure impulse applied at various steady state arterial pressure levels in the range from 160 down to 40 mmHg. The dashed curve shows the prediction, made by the mathematical model for purely myogenic mechanisms designed in Paper III, of the extent to which changes of basal vascular tone and of arterial pressure per se would have altered the magnitude of the myogenic constrictor response, had there been no metabolic interaction with myogenic reactivity. Lower panel: Steady state blood flow values observed at the various arterial pressure levels. The data (referring to skeletal muscle) show an attenuation of myogenic reactivity with decreasing arterial pressure which was present even in the pressure range where blood flow was quite effectively autoregulated.

pressure levels in the range from 160 to 40 mmHg. The lower panel of this figure shows the steady state blood flow values in the muscle observed at these various arterial pressure levels. The fact that the amplitude of the myogenic responses in vivo to the pressure impulse (upper panel, solid curve) were clearly smaller than those predicted by the mathematical model (dashed curve) indicates that some factor(s) other than those incorporated in the design of the model must have interfered

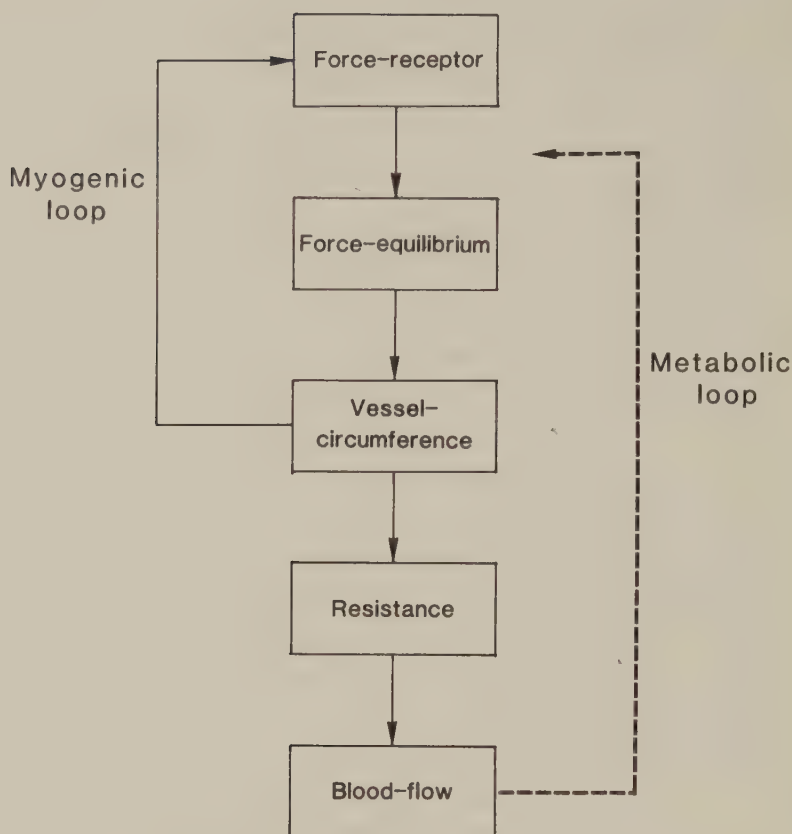


Fig. 6. Schematic block diagram illustrating postulated interaction between myogenic mechanisms and metabolic factors in the local control of vascular resistance. The myogenic loop, responsive to pressure, is essential for the initiation and maintenance of basal vascular tone. The blood flow dependent metabolic feedback conveys the error signal that is necessary for autoregulation of blood flow.

with the myogenic responsiveness, most likely via a blood flow dependent metabolic influence. This hypothesis was subjected to further analysis in Paper IV (see Fig. 5) which included observations during more defined activation of the vascular metabolic control system, viz. during graded very light exercise. The data showed that the attenuation of myogenic reactivity analyzed in terms of the myogenic constrictor response to a pressure impulse during light exercise was quite similar to that during pressure induced blood flow reduction in the resting muscle. This similarity was taken as further support for the view of a significant local metabolic interaction with myogenic mechanisms also during arterial pressure reduction, including the pressure range where blood flow was quite effectively autoregulated.

The interaction between the myogenic and metabolic control systems during autoregulation of blood flow might in view of the results obtained in Paper IV be postulated to be represented by two interacting feedback loops as illustrated in the schematic block diagram in Fig. 6. The myogenic loop to the left is considered to be important for the initiation and maintenance of normal basal tone in the arterial resistance vessels, through the excitatory influences exerted by normal intravascular blood pressure (Grände et al. 1979). Raised or lowered arterial pressure would cause enhancement, or partial withdrawal, of such tonic excitatory influences leading to reinforcement/decrease of myogenic basal vascular tone. The metabolic loop to the right in Fig. 6 would modulate the myogenic control system by altering its 'gain' via direct or indirect effects on the excitation, or excitation-contraction coupling, of the vascular smooth muscle to a given microvascular wall tension stimulus. Note that the myogenic feedback loop receives no direct information about the prevailing blood flow, whereas the metabolic loop, probably sensing the flow dependent 'metabolite' concentration is the one that continuously provides the myogenic control system with the error signal necessary for maintaining blood flow virtually constant. The finding in Paper IV that even the minute changes of blood flow occurring during autoregulation affected myogenic reactivity indicates that the 'gain' in the metabolic loop is high.

4. A theory for the local vascular regulatory mechanisms responsible for autoregulation of blood flow, interpretable on the smooth muscle level (Papers V and VI).

The investigations discussed sofar provided support of the hypothesis that autoregulation of blood flow is accomplished by interaction of microvascular wall tension related myogenic mechanisms and blood flow dependent metabolic factors. The purpose of Paper VI was to test this hypothesis in greater detail. The course of action to achieve this goal was to design a further refined mathematical model for myogenic as well as metabolic control of vascular resistance and to test it for a wide variety of experimental interventions. In vivo data for experimental corroboration were taken from the material in some of our previous investigations (Grände et al. 1977, Grände & Mellander 1978, Grände et al. 1979), further from the material in Paper IV and from some additional experiments performed in Paper VI. Attempts were made to base all

assumptions on established physiological concepts. Since the smooth muscle is the effector unit in vascular control, a mathematical model for the contractile machinery of vascular smooth muscle was also designed (Paper V) and included in the model presented in Paper VI.

The vascular smooth muscle model was based on the conventional sliding filament theory (H.E. Huxley 1953, H.E. Huxley & Hansson 1954, A.F. Huxley & Niedergerke 1954), and on the idea that muscle force is produced by the cross-bridges extending from the myosin to the actin filaments (A.F. Huxley 1957). There are two additional key assumptions in the model:

- a) Due to the large number of active cross-bridges in a muscle their combined action can be adequately described by an average cross-bridge function. Thus, all calculations were made with respect to the average cross-bridge and not to a continuous spectrum of cross-bridges in different functional states.
- b) The transfer of energy via the cross-bridges extending from the myosin to the actin filaments takes place via a self-regulated 'friction clutch' mechanism. The term self-regulated reflects the assumption that the efficiency of the coupling depends on the average cross-bridge load, i.e. the 'friction clutch' mechanism constitutes a feedback system, the efficiency of which depends on its input (cf. Caplan 1966).

It was shown in Paper V that a mathematical formulation of the above assumptions gave rise to a simple dynamic muscle model which in great detail was able to reproduce many different experimental in vitro observations on vascular smooth muscle. Special mention should be made that the model could account for some mechanical findings that recently have attracted increasing attention. These include a non-hyperbolic force-velocity relationship at high forces (cf. Hellstrand & Johansson 1979) and the ability of smooth muscle to maintain isometric force in conditions of a reduced maximum contraction velocity (cf. Dillon & Murphy 1982). The model also predicted a 'yield' at forces greater than the control force when subjected to imposed stretch (cf. biological observations by Johansson 1983), a feature important for the interpretation of the microvascular resistance response to a transmural pressure impulse stimulus (cf. Figs 4 and 8).

The simplicity of this muscle model and its ability to reproduce many

disparate experimental findings on vascular smooth muscle mechanics (Paper V) seem to justify the above mentioned simplifying assumptions made in the derivation of the model. In its simpler form where an initial fast velocity transient (<100 ms) was neglected, the muscle model description reduced to one differential and two algebraic equations which were easily included in the further analysis of the local control of vascular resistance (Paper VI).

The mathematical model for the local control of vascular resistance during autoregulation of blood flow (Paper VI) was designed so as to simulate the reactions in the vascular bed of the lower leg muscles in cats. Like the models presented in Papers II and III it permitted differentiation between the resistance responses in the 'proximal arterial vessels', the 'microvessels' and the 'large veins'. For details of the design of the model, see Appendix.

It has been established that both the proximal and the microvascular sections are regulated by myogenic mechanisms (cf. Grände et al. 1977) and that these mechanisms are modulated by metabolic factors (cf. Paper IV). These two vascular sections are thus treated mathematically in an analogous manner, and the following assumptions were made:

- a) The microvascular myogenic receptor mechanism, exhibiting both static and dynamic properties, was assumed to be a slowly-adapting force receptor (cf. Sokolove 1972), which during excitation causes an influx of Ca^{2+} exponentially related to the excitation level.
- b) The proximal arterial myogenic receptor mechanism was assumed to show no adaption because of the slow reactivity pattern in this section (cf. Grände et al. 1977). The resulting delay in tension development was taken into account in terms of a propagation process over the considerable length of these vessels.
- c) In addition to the myogenic calcium influx, an influx that is not sensitive to force, was assumed.
- d) The level of intracellular activator calcium in both vascular sections was assumed to determine the relative number of activated cross-bridges in the contractile machinery of the vascular smooth muscle (cf. Paper V).
- e) The contractile machinery was represented by the model for vascular smooth muscle presented in Paper V.

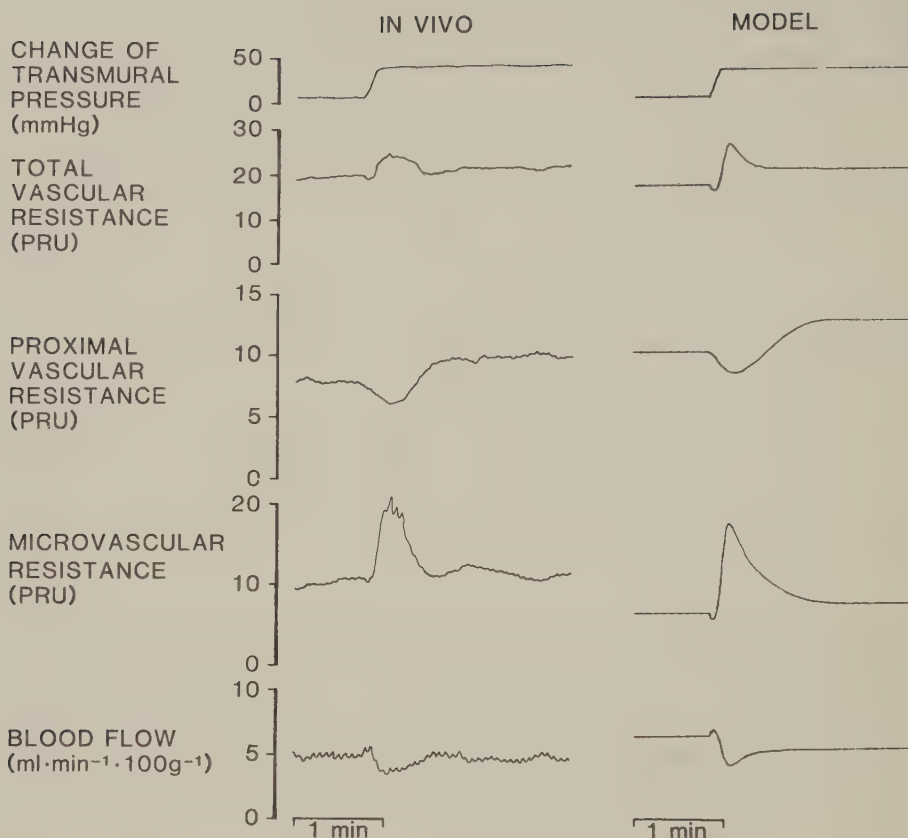


Fig. 7. Experimental corroboration of the mathematical model (Paper VI) designed for description of local myogenic and metabolic control of vascular resistance in skeletal muscle. The model (see right panels) was able to simulate total and segmental vascular resistance responses and blood flow changes in vivo (see left panels) evoked in response to an increase in vascular transmural pressure (30 mmHg) applied at a rate of 3.75 mmHg/s. Note that both the in vivo and model curves showed a dynamic component of the resistance response which was solely confined to the microvessels whereas the static component was present also in the proximal arterial vessels. The fact that the partitioning of resistance in the two vascular sections in the control situation was different in model prediction is explained in text.

f) The metabolic vascular control was described according to the 'vasodilator theory' implying that the interstitial concentration of vasoactive dilator metabolites affects the smooth muscle; such influence was assumed to primarily interfere with the excitation-contraction coupling of vascular smooth muscle, but also with its shortening velocity.

g) The large vein section was considered to show merely passive-elastic characteristics (cf. Mellander & Johansson 1968).

Following parameter estimation (Paper VI), the model's capability to predict locally controlled vascular reactions was tested for a variety of experimental interventions, such as change of transmural, arterial, as well as venous pressures. These tests considered the dynamic (transient) characteristics in total and segmental vascular resistance behaviour as well as the typicals of the steady state responses. Fig. 7 illustrates the ability of the model to simulate an overall vascular transmural pressure ramp increase of 30 mmHg. The left panels show the resulting effects on in vivo resistance of such a pressure change as recorded in the whole vascular bed of skeletal muscle and in its 'proximal' and 'microvascular' segments, as well as the effect on total regional blood flow. It can be seen that with regard to the whole vascular bed the pressure stimulus caused a transient dilatation which was followed by a dynamic myogenic constriction with a maximum reached about 15 s after the onset of the stimulus. The resistance then declined to a steady state level about 15% above the control. The dynamic myogenic constriction was solely confined to the microvessels, whereas the proximal section responded with a more prolonged dilatation. Most of the static (steady state) resistance response to the increased transmural pressure was confined to the 'proximal' vascular section. The right panels in this figure show corresponding tracings obtained with the model. These registrations demonstrate that the model with quite good accuracy could simulate the total as well as the segmental resistance responses in the vascular bed to a transmural pressure ramp increase of 30 mmHg with regard to both the dynamic and the static characteristics. The lower right tracing shows the model prediction of how blood flow was influenced by this transmural pressure increase, which was very similar to the in vivo situation. It should be noted that the difference between in vivo and model curves as regards the partitioning of the segmental resistances in the control situation does not reflect on the ability of the model to simulate the in vivo situation. The reason is that the control values in the model represented mean values taken from a previous study (Grände et al. 1977), and that they thereby were fixed, whereas there was a substantial spread in the biological material from which the left panel is just one example.

The model was also able to simulate the in vivo reaction to an impulse pressure stimulus which is illustrated in Fig. 8. The left panels of this figure show, at an arterial pressure level of 150 mmHg, the in vivo

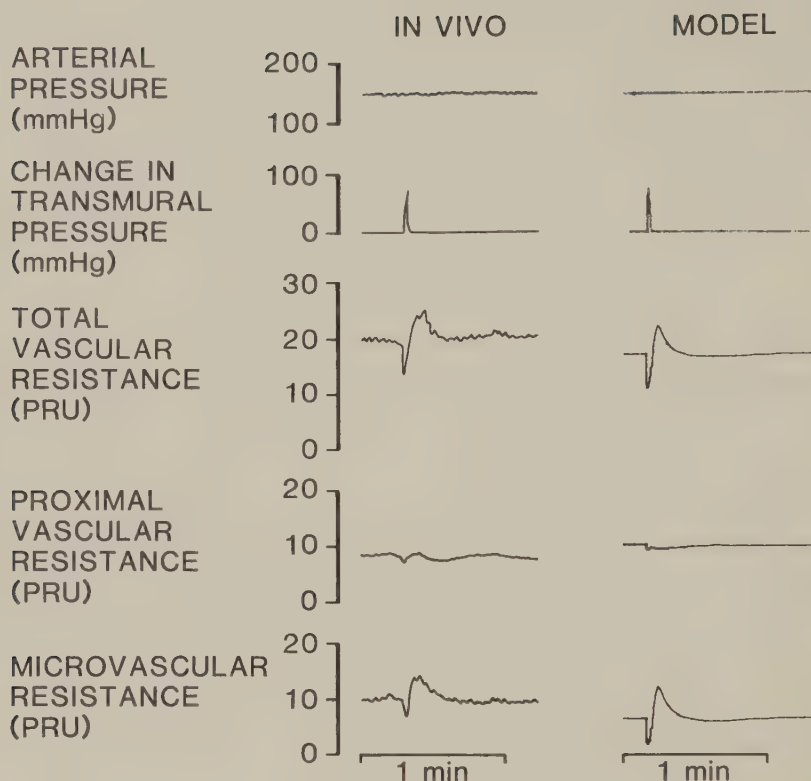


Fig. 8. Comparison of myogenic vascular resistance responses evoked by a transmural pressure impulse with a duration of 2 s and an amplitude of 75 mmHg applied at normal arterial pressure as predicted by the model designed in Paper V (right panels) and as observed in vivo (left panels). Note the close similarity between in vivo and model curves both concerning the general response pattern as well as the confinement of the dynamic myogenic constrictor response to the microvessels. The model explanation for the initial decline in resistance is a 'yield' in the contractile machinery of the vascular smooth muscle and the model explanation for the constriction is a purely myogenic reaction.

resistance effects of such a pressure impulse with a duration of 2 s and an amplitude of 75 mmHg, as recorded in the whole vascular bed ('total vascular resistance'), and in its 'proximal arterial' and 'microvascular' segments. These tracings show that, with regard to total resistance, the pressure impulse caused an almost instantaneous decrease, the model explanation for which is a yield in the contractile machinery, followed by a resistance increase of about 5 PRU above the control level. This myogenic constrictor response was confined to the microvessels as can be seen from the lower left registration in this figure. The right panels show corresponding computer tracings and it can be seen that the model could mimic, with quite high fidelity, the in vivo responses both

concerning the confinement of the response to the microvessels as well as the general time characteristics. The model interpretation of the pressure impulse constrictor response is a rapid increase in the myogenic receptor force giving a transient but quite pronounced increase in the intracellular Ca^{2+} level, which is over within a few seconds, whereafter the delayed myogenic constriction develops. The amplitude of the myogenic constriction depends to a great extent on the shortening velocity of the smooth muscle. This is why the resistance response to a pressure impulse in the model simulation is absent in the proximal section, where the contraction velocity in the parameter estimation of the model was found to be some 10 times lower than in the microvessels. The model further predicted that the active microvascular constrictor response to a pressure impulse was purely myogenic in nature, uninfluenced by metabolic factors. This corroborated the suggestion made in Paper IV that the amplitude of the constrictor response to a pressure impulse is a good measure of myogenic reactivity.

The model was also tested for vascular reactions to venous pressure changes which is illustrated in Fig. 9. This figure shows how, at a mean arterial pressure of 100 mmHg, a ramp increase in venous outflow pressure of 20 mmHg exerts an influence on 'total' vascular resistance, and on resistance in the 'proximal' and 'microvascular' segments. The lower left tracing shows the simultaneously recorded blood flow. It can be seen that the venous pressure stimulus with regard to the whole vascular bed caused a transitory dynamic constriction whereafter the vascular bed dilated to a level some 5% below control. As can be seen from the Fig. the dynamic constriction was entirely confined to the microvessels. Underlying the subsequent static steady state dilatation in the whole vascular bed there was, surprisingly, a slight constriction in the proximal arterial and a dilatation in the microvascular section, the net result of which was a decrease in total vascular resistance. The dilatation due to the venous pressure elevation was, however, not sufficient to autoregulate blood flow as shown in the lower left recording. The right panel shows corresponding computer curves and it can be seen that the in vivo and model curves were quite similar. The transitory dynamic constriction was thus present in the model and confined to the microvessels as in vivo. It can also be seen that underlying the static dilatation in the whole vascular bed there was also in the model a dilatation in the microvascular section. At first sight it might seem surprising that the

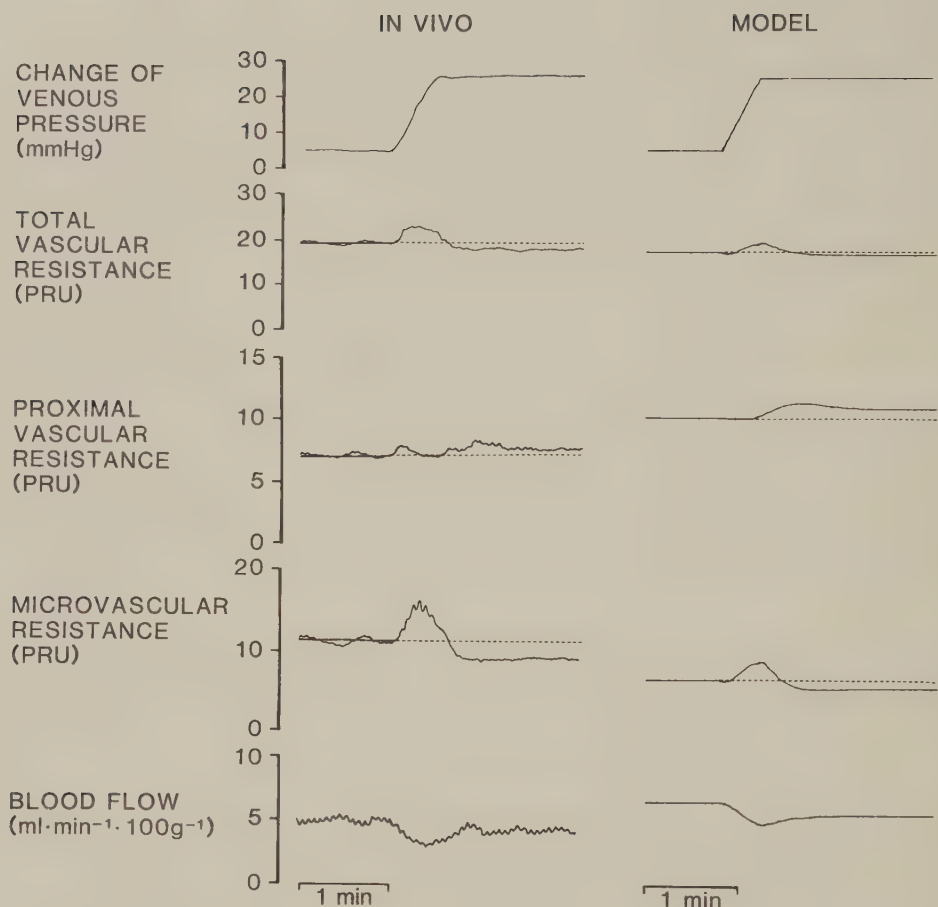


Fig. 9. In vivo experiment illustrating the effects of an elevation of venous outflow pressure by 20 mmHg on vascular resistance and blood flow in skeletal muscle (left panels). The right panels show corresponding model predictions. It can be seen that, apart from the partitioning of control resistance in the two different vascular sections, the model and in vivo curves showed the same pattern of response. The dynamic myogenic constriction was thus, both in vivo and in the model, confined to the microvessels. In the steady state of constant increased venous pressure, the microvessels dilated slightly, whereas the proximal arterial vessels responded with a weak constriction, the net result of which was a dilatation in the whole vascular bed.

microvessels dilate and the proximal vessels constrict upon venous pressure elevation. However, this phenomenon could be ascribed in the model to the fact that the myogenic stimulus in the microvessels was not capable of maintaining a vascular constriction due to the simultaneous presence of strong metabolic feedback influence. The proximal vessels were, however, able to maintain a weak constriction due to the lack of sufficient metabolic feedback in this vascular section.

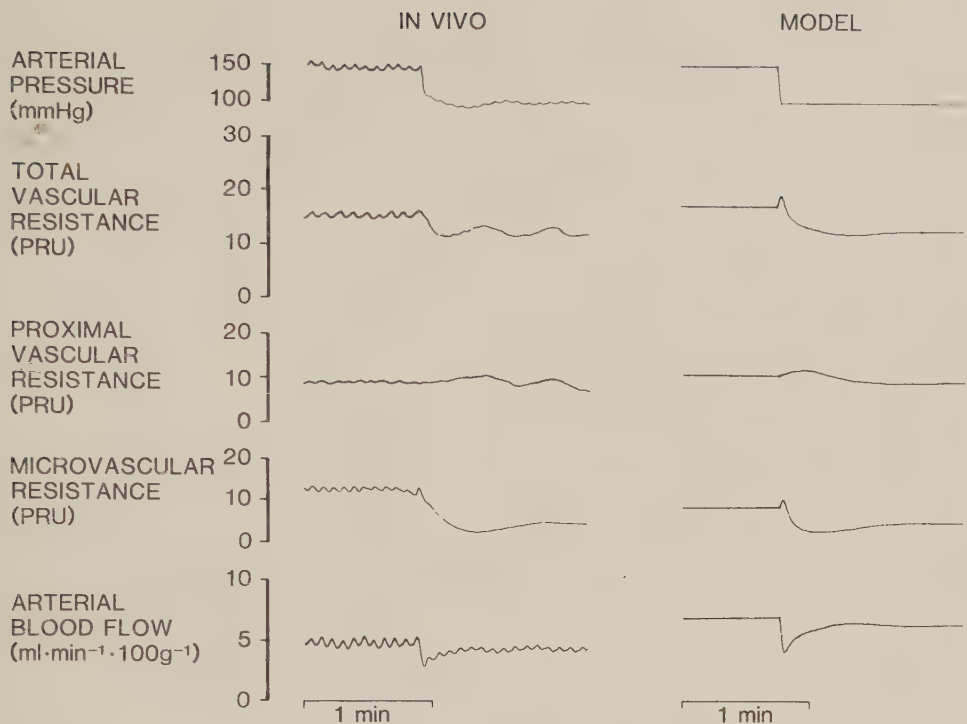


Fig. 10. The effects of a reduction of arterial inflow pressure from 150 to 100 mmHg on vascular resistance and blood flow in vivo (left panels) and as predicted by the model (right panels). Note that, for both in vivo and model curves, the active autoregulatory dilatation was confined to the microvessels, whereas that proximal vascular resistance was almost unaffected by the pressure change. The lower tracings illustrate that the model predicted about the same degree of autoregulation of blood flow at this arterial pressure reduction as in vivo.

The ability of the model to simulate vascular resistance responses to arterial pressure changes is shown in Fig. 10 which is a representative registration of effects evoked at an arterial pressure reduction from 150 down to 100 mmHg. It can be seen that this pressure decrease caused an active dilatation in the whole vascular bed. The dilatation was entirely confined to the microvessels whereas resistance in the proximal arterial vessels was maintained almost unchanged. The lower left panel shows that there was a fairly well developed autoregulation of blood flow in this arterial pressure range. The right panels show that the model, with quite good accuracy, could reproduce this experimental situation. The active dilatation in the model was thus confined to the microvessels and the blood flow autoregulatory capacity was about the same as in vivo.

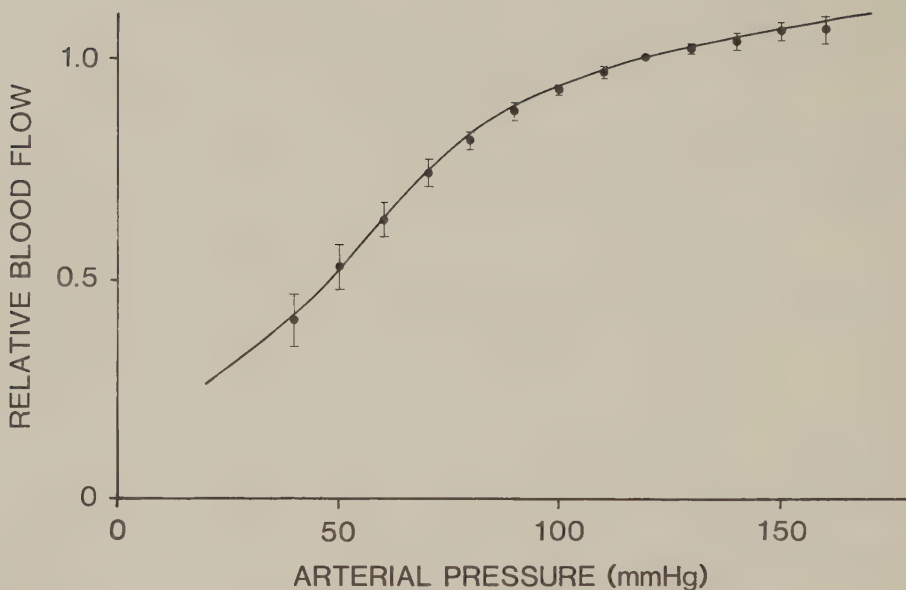


Fig. 11. The solid line shows the steady state blood flow values, expressed in relative terms, predicted by the model, at different mean arterial pressure levels in the range from 180 to 20 mmHg. Corresponding in vivo data (6 experiments) are shown as vertical bars indicating 95% confidence intervals. It can be seen that the model predicted the same degree of autoregulation of blood flow in the 'autoregulatory' pressure range (above about 90 mmHg) and also similar decline of blood flow below this pressure level as observed in the in vivo situation.

This is illustrated in detail in Fig. 11 which depicts steady state blood flow in relative terms (flow at 120 mmHg arbitrarily set to unity) as a function of arterial inflow pressure in the range from 160 down to 40 mmHg. The vertical bars in this figure indicate 95% confidence intervals for 6 in vivo experiments and the solid curve was obtained with the mathematical model. It can be seen that the model prediction in all respects was very similar to the in vivo data, with a fairly well developed autoregulation of blood flow in the arterial pressure range above about 90 mmHg.

These results demonstrate that the model has the ability to match simultaneously the constraints imposed by a variety of experimental observations, as exemplified here by its capability to simulate dynamic as well as static resistance responses to overall transmural pressure, venous pressure, and also arterial pressure, stimuli. With such characteristics the presented model analysis strengthens the tested hypothesis that myogenic reactions are important for the initiation and maintenance of basal vascular tone and further that myogenic reactions are being constantly modulated by blood flow dependent metabolic factors, for instance in autoregulation of blood flow.

DISCUSSION

The studies summarized in this paper deal with the local myogenic and metabolic control of vascular resistance in cat skeletal muscle with special emphasis on the mechanisms underlying the vascular adjustments in autoregulation of blood flow. The complexity of these control systems makes sometimes direct interpretation of biological observations impossible and the approach in these studies was therefore to design mathematical models which could be used as tools to facilitate the process of making exact predictions of proposed hypotheses.

A first mathematical model was formulated in Paper II with the purpose, among other things, to test the hypothesis that myogenic vascular responses are directly related to and triggered by vessel wall tension and its rate of change. The myogenic control system by itself is quite complex including many non-linear factors inherent, for instance, in the laws of Laplace and Poiseuille. This makes it very difficult to predict the consequences of wall tension related myogenic mechanisms in the control of vascular resistance responses in vivo to transmural pressure stimuli. The results obtained with the model, which in its design incorporated the non-linear factors mentioned, strongly corroborated the hypothesis of wall tension related myogenic mechanisms in the local vascular control. A second important advantage in modeling is that it can provide estimation of variables which are difficult or impossible to directly assess by biological experiments. This was exemplified in Paper II where changes of wall tension and its rate of change as well as of vessel radius could be predicted continuously during the reactions evoked by phasic and static change of overall vascular transmural pressure. This provided some new insight into the operation of the myogenic vascular control system. The model thus contradicted some preconceived ideas about myogenic regulation and indicated, for instance, that wall tension is not the controlled variable per se in myogenic regulation, since wall tension was found to remain at a value above control during the phase of developed myogenic vessel lumen reduction evoked by a pressure rise. This finding does, however, not imply that wall tension is an unimportant variable in vascular control, since it is the trigger of myogenic reactions.

The more refined model presented in Paper III provided further

applicability to the interpretation of biological phenomena. For instance, it could predict the extent to which the amplitude of a constrictor or dilator response to a given stimulus is influenced by the level of vascular tone prevailing prior to the stimulus. This phenomenon which is of great importance for any quantitative evaluation of constrictor or dilator responses in the resistance vessels, could be ascribed to a great extent to physical factors inherent in the laws of Laplace and Poiseuille. Practical examples of the use of this model for such analyses were given in Papers III and IV. In the latter, such model analysis greatly aided in the estimation of the blood flow dependent metabolic interaction with myogenic reactivity over a wide range of arterial pressures where considerable changes in vascular tone take place.

The aim of the analysis performed in Paper VI was to test the hypothesis that autoregulation of blood flow in skeletal muscle is accomplished by wall tension related myogenic regulatory mechanisms operating under continuous interaction from flow dependent metabolic factors. Such simultaneous interaction of two control systems makes it even more difficult to correctly interpret the biological observations. Modeling can in this context be useful since it provides a means of repetitive rejections and subsequent improvement of the proposed theory until satisfying biological corroboration is obtained (cf. Fig. 1).

The model presented in Paper VI was principally based on the same series-coupled vessel arrangement and on the same basic concepts for the myogenic control system as elaborated and established in the previous models (Papers II and III). In this refined model design, the hypothesis of a flow dependent metabolic interaction with myogenic mechanisms via a feedback effect on the excitation-contraction coupling of vascular smooth muscle, as suggested in Paper IV, was adopted. It further incorporated the contractile muscle machinery model from Paper V to make predictions interpretable on the cellular/subcellular level. Attempts were also made to use mathematical formulations for the biological events of least possible complexity, still maintaining greatest possible applicability of the model.

There was a close resemblance between observed reactivity patterns in vivo and the model predictions of myogenic and metabolic interaction

during a wide variety of constraints, as described in Results. With such characteristics the model was considered adequate for further analysis of fundamental principles in autoregulation of blood flow.

Such a model analysis of autoregulation of blood flow, is presented in Fig. 12 which shows some possible underlying cellular events. In the analysis the arterial inflow pressure in the model was decreased from 160 down to 20 mmHg at a very slow rate (0.01 mmHg/s) so that the control systems could be considered to be at steady state equilibrium at all times during the pressure change.

Fig. 12, panels A, thus depicts the model predictions of myogenic receptor force (expressed in relative terms) in the proximal arterial section (left panel) and in the microvascular section (right panel). It can be seen that the relative decrease in receptor force with decreasing arterial pressure is more pronounced in the proximal arterial section than in the microvascular section. Thus, in the pressure range from 160 down to 60 mmHg there was a decline in relative force in the proximal vessels of about 80% whereas in the microvascular section it was only about 60%. These curves suggest that wall tension (force) is not the controlled variable in autoregulation of blood flow as proposed by some previous authors (e.g. Johnson 1974, Johnson & Wayland 1967, Koch 1964, Thurau 1964). This unloading of the myogenic receptor results in a reduction of the force-dependent Ca^{2+} influx into the effector cells (panels B) which depict the relative level of intracellular Ca^{2+} in the two vascular sections as a function of arterial inflow pressure. From these panels and the data in panels A it can be seen that not all of the intracellular calcium is myogenic in nature (i.e. force dependent), since about 50% of the calcium still remains after the quite marked reductions of myogenic receptor force. The model thus predicted that of the intracellular calcium responsible for the basal vascular tone, at an arterial pressure of 150 mmHg, approximately 50% is myogenic in nature. Despite the more pronounced reduction in relative force in the proximal vessels it can be seen that the decrease in Ca^{2+} influx in relative terms is of the same order of magnitude in the two vascular sections which, in combination with the data in panels A, can be interpreted as a higher 'gain' of the myogenic control system in the microvascular section. As illustrated in panels C, the level of Ca^{2+} is affecting the excitation-contraction coupling, and thus the active force developed by

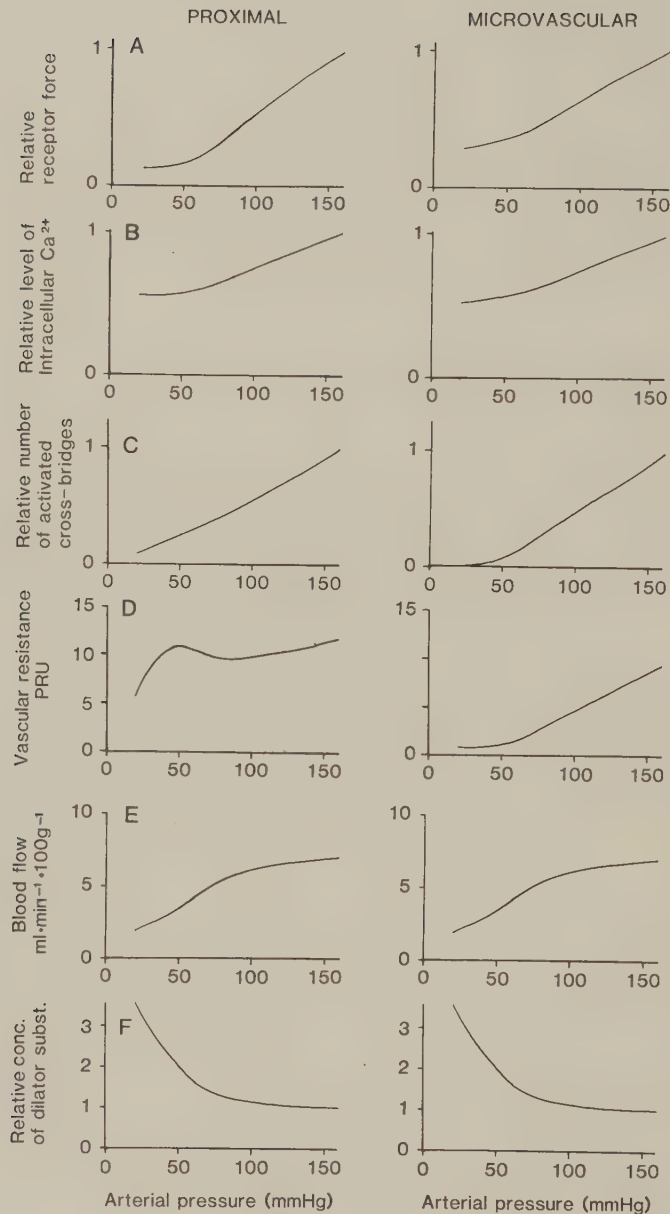


Fig. 12. Model predictions of some variables in local vascular control that are unmeasurable with current experimental techniques, viz. myogenic receptor force, level of intracellular Ca^{2+} , number of active cross-bridges in the contractile machinery of the vascular smooth muscle, and interstitial concentration of the dilator substance(s), all expressed in relative terms. Data refer to 'proximal arterial vessels' and arterial microvessels. These variables are compared to predictions of vascular resistance and blood flow during gradual decrease in arterial pressure at low rate (abscissa). This model description of the interrelationships between these events provides a tentative explanation of the mechanisms underlying autoregulation of blood flow in skeletal muscle, see text.

the contractile machinery of the vascular smooth muscle. These panels show the relative number of activated cross-bridges, reflecting active forces, in the two sections during reduction of the arterial inflow pressure. It can be seen that the reduction in active force is greatest in the microvascular section. This can be explained by a stronger blood flow dependent metabolic feedback on myogenic tone in this vascular section. These panels also show that the metabolic feedback influences the active smooth muscle force that is not myogenic in nature since the curves depicting the number of activated cross-bridges continue to decrease despite the fact that the concentration of intracellular calcium has levelled off at an arterial pressure of about 50 mmHg (panels B). The decrease in active muscle force causes the vessels to dilate as can be seen from panels D which depict pressure induced changes of vascular resistance in the two sections. The more marked decrease in active force in the microvascular section results, as expected, in a pronounced microvessel dilatation, whereas the proximal arterial vascular section dilates only slightly and even tends to constrict in the arterial pressure range below about 80 mmHg. This constriction can be ascribed to the lower myogenic 'gain' in combination with relatively weak metabolic influence in these vessels, i.e. the unloading of the proximal vessels (decrease in arterial pressure) does not reduce the number of activated cross-bridges sufficiently to accomplish dilatation. When blood flow becomes seriously restricted, however (i.e. at an arterial pressure level below about 50 mmHg), the consequent greater activation of metabolic control system manifests itself as a clearcut dilatation. The described active adjustments of vascular resistance accomplish a fairly well developed autoregulation of flow in the arterial pressure range from 160 down to about 90 mmHg (panels E). In this autoregulatory pressure range, the concentration of the metabolic dilator substance(s), mediating the effects of the metabolic vascular control system, is kept virtually constant (panels F). The circumstance that during autoregulation of blood flow the metabolite concentration is maintained virtually constant by the local regulatory system, makes experimental identification of responsible dilator substance(s) in vivo quite difficult. This is in contrast to other circulatory adjustments, such as exercise hyperemia, when the greatly increased tissue metabolism raises the concentrations of the metabolic dilator substances to such high levels that the change may be easily detected in the effluent blood from the capillaries.

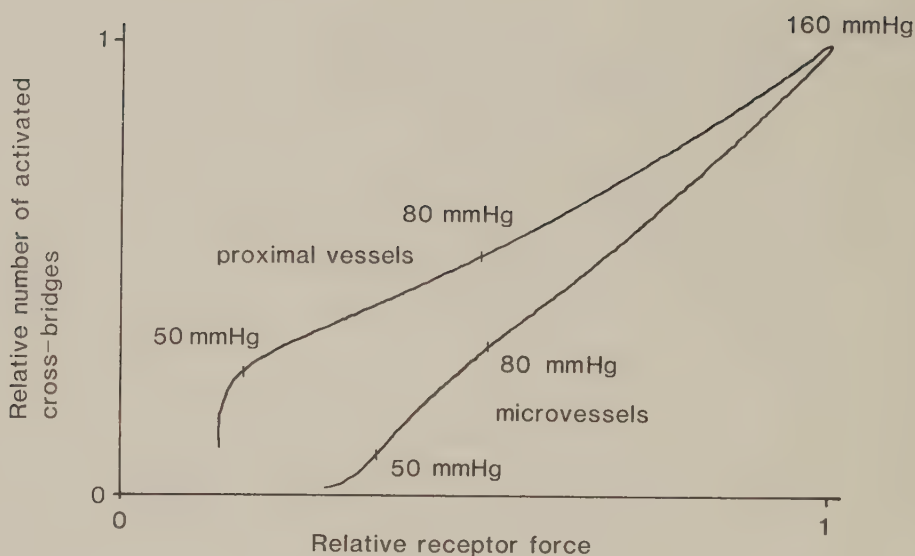


Fig. 13. Model predictions of the number of active cross-bridges plotted versus the myogenic receptor force (data expressed in relative terms) in the 'proximal arterial' and 'microvascular' sections during gradual reduction of arterial pressure. The values inserted in the Fig. refer to the level of arterial pressure. The slope of these curves is a measure of the 'net gain' in the myogenic control resulting from simultaneous interaction by metabolic factors. It can be seen that the 'myogenic net gain' in the microvessels is higher than in the more proximal vessels in the pressure range from 160 down to 50 mmHg. Below this pressure, the metabolic control starts to manifest itself in the proximal arterial vessels.

The delicate synergistic interaction between myogenic and metabolic regulatory mechanisms in autoregulation of blood flow might be better visualized in Fig. 13. It depicts the active myogenic force of the smooth muscle effectors in terms of the relative number of activated cross-bridges as a function of the relative myogenic receptor force in the proximal arterial and microvascular sections, when arterial inflow pressure was reduced from 160 down to 20 mmHg. The numbers inserted in the figure refer to the level of arterial pressure. It can be seen that myogenic gain modulated by metabolic factors, the 'net myogenic gain' (i.e. the slope of these curves), is higher in the microvessels than in the proximal arterial vessels in the arterial pressure range from 160 down to about 50 mmHg. In the pressure range between 80 and 50 mmHg the 'net myogenic gain' in the microvessels increases further due to the decrease in blood flow and the thereby increased metabolic interaction. At a pressure of 50 mmHg the microvessels are almost maximally dilated whereas the proximal arterial vessels still have considerable tone. In the proximal arterial vessels the metabolic feedback is quite weak until

blood flow becomes seriously restricted at a pressure level of about 50 mmHg below which the 'net myogenic gain' decreases drastically, leading to pronounced dilatation also in these vessels.

Autoregulation of blood flow in skeletal muscle can thus tentatively be explained by wall tension related myogenic mechanisms being synergistically interacted upon by blood flow dependent metabolic factors. These factors affect the efficacy of a given intracellular level of Ca^{2+} in generating active smooth muscle force. The most distal arterial microvessels have the highest 'myogenic gain' and these vessels are also the most sensitive ones to metabolic factors.

GENERAL SUMMARY

This study aimed at formulating a comprehensive theory for local myogenic and metabolic control of vascular resistance in cat skeletal muscle during autoregulation of blood flow.

1. The experimental observations of vascular resistance in vivo were obtained with a whole-organ technique. With the aid of a pressure gradient flowmeter and a vascular resistance meter, continuous recordings were provided of vascular resistance in the whole vascular bed and in its consecutive segments, the 'proximal arterial vessels', the 'microvessels', and the 'large veins'. To be able to make exact predictions of postulated hypotheses for the operations of these complex regulatory systems, mathematical models were designed. To derive confidence in the proposed model, the model predictions were tested for a variety of different experimental interventions in terms of change of overall vascular transmural pressure, venous pressure, as well as arterial pressure.
2. The pattern of dynamic and static myogenic reactivity as studied directly on single arterioles with a vital microscopic technique was very similar to that studied with the more indirect whole-organ technique. This finding justified the use of whole-organ observations in vivo for experimental corroboration of model predictions and, hence, validations of the proposed theories.
3. A mathematical model was designed to describe purely myogenic, static and dynamic responses in the microvessels to change of overall vascular transmural pressure. It was based on a force-equilibrium in the microvessel wall, including passive forces related to vascular transmural pressure (Laplace's law), wall elasticity and wall viscosity, and an active force related to resting vascular tone, as well as the active static and dynamic myogenic forces. The model analysis strengthened the view that myogenic reactions in vivo are related to and triggered by vascular wall tension (force) and its rate of change. The model further could predict the extent to which non-linear physical factors inherent, for instance, in the laws of Laplace and Poiseuille, influenced the myogenic responses in vivo when observed at different levels of vascular tone and intravascular pressure.
4. When arterial pressure was varied in the range from 160 down to 40 mmHg, myogenic mechanisms were found to be attenuated by other factors

than the physical ones. Such attenuation could be ascribed to a flow dependent metabolic interaction with myogenic reactivity which was present even in the pressure range where blood flow was autoregulated quite effectively.

5. To test the hypothesis that myogenic mechanisms are constantly being modulated by blood flow dependent metabolic factors during autoregulation of blood flow, a refined mathematical model was designed. This model was also made interpretable on the cellular level by including the developed model for the contractile machinery of vascular smooth muscle.

6. In the muscle model it was proposed that the average transfer of energy via the cross-bridges extending from the myosin to the actin filaments takes place via a self-regulated 'friction clutch' mechanism. This gave rise to a simple model for the contractile machinery of vascular smooth muscle which in great detail predicted experimental observations of smooth muscle mechanics under isotonic as well as isometric conditions. This model, without any ad hoc assumptions, thus displayed a non-hyperbolic force-velocity relationship in the high-force portion of the curve, and it was able to maintain isometric force in conditions of a reduced maximum contraction velocity.

7. In the integrated model, for local regulatory mechanisms, the proximal arterial and microvascular sections were considered to be regulated by myogenic and metabolic mechanisms. The myogenic mechanisms were described in terms of a slowly adapting force receptor, the excitation level of which influenced the concentration of intracellular activator calcium in the vascular smooth muscle. Vascular metabolic control was described according to the 'vasodilator theory' implying that the interstitial concentration of dilator substances mediates the metabolic influence. The metabolic control was assumed to exert its main influence by shifting the Ca^{2+} -force relationship of the contractile machinery, i.e. modulating the excitation-contraction coupling of vascular smooth muscle. Strong experimental corroboration of the model predictions of vascular responses to a variety of pressure stimuli lent strength to the proposed hypothesis of metabolic feedback interaction on myogenic mechanisms during autoregulation of blood flow.

APPENDIX

DESIGN OF THE MODEL PRESENTED IN PAPER VI

The model designed in Paper VI is here briefly summarized excluding all derivations. The equations presented are for reasons of consistency given the same numbers as in the original paper.

The vascular bed is represented by three series-coupled vascular sections: The proximal arterial, the microvascular, and the large vein section. The two first mentioned are considered to be regulated by myogenic and metabolic mechanisms whereas the large vein section is assumed to have merely passive properties.

Mean distending pressure in the proximal, P_{dp} , microvascular, P_{dm} , and large vein, P_{dv} , vascular sections can according to Fig. 1 be defined as

$$P_{dp} = (P_A + P_{SA})/2 + P_T, \quad (1)$$

$$P_{dm} = (P_{SA} + P_{SV})/2 + P_T, \quad (2)$$

and

$$P_{dv} = (P_{SV} + P_V)/2 + P_T, \quad (3)$$

where P_T is the overall vascular transmural pressure.

The inflow pressure to the microvascular section, P_{SA} , and to the large vein section, P_{SV} , can be expressed in the following way

$$P_{SA} = (P_A - P_V) \frac{R_m + R_V}{R_p + R_m + R_V} + P_V, \quad (4)$$

and

$$P_{SV} = (P_A - P_V) \frac{R_V}{R_p + R_m + R_V} + P_V, \quad (5)$$

where R_p , R_m , and R_V are the vascular resistances in the proximal, microvascular and large vein sections respectively (to be defined below).

MECHANICAL PROPERTIES OF THE VESSEL WALL

Vessel wall geometry

Incompressibility is assumed for the vessel walls and the following expressions thus apply for the thickness of the tension sustaining media, h_m , and for the intima, h_i , which is assumed to sustain no tension:

$$h_m = h_{m1} \frac{r_1}{r}, \quad (6)$$

and

$$h_i = r - \frac{h_m}{2} - \sqrt{\left(r - \frac{h_m}{2}\right)^2 - h_{i1}(2r - h_{m1} - h_{i1})}, \quad (7)$$

where r is the radius at the line of force; and h_{m1} and r_1 are constants (index 1 refers to a vessel state with normal vascular tone and normal arterial and venous pressure). The resistance of the vascular section can now be defined according to Poiseuille's law as

$$R = C_R \frac{L}{r_i^4}, \quad (8)$$

where C_R is a constant; L the length of the vascular section and; r_i the internal radius which in turn is defined as

$$r_i = r - h_i - \frac{h_m}{2}. \quad (9)$$

Contractile machinery

The smooth muscle model, presented in Paper V, is used for the description of the contractile machinery. This model includes three elements: (1) an active contractile component (CC), (2) an external elastic component coupled in series with the CC, and (3) an elastic component inserted in parallel with the first two components. The transfer of force (energy) from the active cross-bridges to the actin filaments is assumed to take place via a 'friction clutch' mechanism. Hence we obtain

$$\dot{x} = \frac{F_{cc}}{n_c f_c} - v_c, \quad (10)$$

where F_{cc} is the total active force of the contractile component; n_c the

relative number of active cross-bridges (see below); f_c the 'friction' related to an average cross-bridge interaction; v_c the average velocity of the cross-bridge displacement; and $\dot{x}$ the resulting contraction velocity of the contractile component.

The cross-bridge elasticity is assumed to be linear with a stiffness k_c . Thus, the active force sustained by the cross-bridges can be expressed as

$$F_{cc} = n_c k_c h_c, \quad (11)$$

where h_c denotes the average extension of the cross-bridge.

The friction of an average cross-bridge interaction, f_c , is assumed to depend on the energy contained in the cross-bridge elasticity which in turn is dependent on the extension (h_c) squared. Hence we obtain

$$f_c = f_o \exp[b_f(1 - (\frac{h_c}{h_0})^2)], \quad (12)$$

where f_o , b_f , and h_0 are constants.

The velocity of the cross-bridge displacement, v_c , is assumed to depend on the extension of the average cross-bridge, h_c , in the following way:

$$v_c = a_v l_0 \exp[b_v(1 - \frac{h_c}{h_0})], \quad (13)$$

where b_v and l_0 are constants; and a_v , being a measure of v_{max} , is a function which can be influenced by the concentration of metabolic dilator substances (see below).

The number of active cross-bridges, n_c , is determined, firstly, by the degree of activation, n_a , (see below) and, secondly, by the length-active force relationship for the smooth muscle which is defined as

$$n_1 = 1 - a_1 |1 - \frac{x}{l_0}|^{b_1}, \quad (14)$$

where a_1 and b_1 are constants; x the length of the contractile element; and l_0 the optimum muscle length.

The total number of active cross-bridges can now be defined as

$$n_c = n_a n_l. \quad (15)$$

The extracellular portion of the series elastic component is, in the present model, assumed to be linear, i.e. the extension is proportional to the active force F_{cc} . Thus,

$$F_{cc} = k_s h_s, \quad (16)$$

where k_s is the stiffness; and h_s the extension of the extracellular series elastic component.

The stiffness of the parallel elastic component is assumed to be exponential, and its load, F_p , was expressed as

$$F_p = \frac{C_p}{a_p} [\exp(a_p 2\pi(r - r_0)) - 1], \quad (17)$$

where a_p , C_p , and r_0 are constants; and r the vessel radius at 'the line of force'.

Force equilibrium in the vessel wall

The proximal and microvascular sections. The active force (F_{cc}) and the force in parallel (F_p) of the vascular smooth muscle are assumed to be balanced by a force, F_d , resulting from the transmural pressure, which according to Laplace's law can be defined as

$$F_d = - L P_d r, \quad (18)$$

where L is the length of the vessel; P_d the mean distending pressure; and r the radius at the 'line of force'. A force equilibrium for a vascular section can now be stated as

$$F_d + F_{cc} + F_p = 0. \quad (19)$$

The large vein section. Myogenic and metabolic mechanisms were neglected in the large vein section and the 'transmural pressure force' (F_{dv}) in this section was assumed to be balanced solely by an

exponential passive elastic force, F_{pV} , defined by

$$F_{pV} = \frac{C_{pV}}{a_{pV}} [\exp (a_{pV} 2\pi(r_V - r_{V0})) - 1] , \quad (20)$$

where C_{pV} , a_{pV} and r_{V0} are constants; and r_V the venous vessel radius at 'the line of force'. This gives the following force equilibrium for the large vein section:

$$F_{pV} + F_{dV} = 0. \quad (21)$$

MYOGENIC CONTROL

Force receptor

The myogenic receptor in the proximal section is assumed to be situated distally in its most reactive part wherefore the pressure at the receptor, P_{rp} , equals P_{SA} . The microvascular myogenic receptor is also assumed to be situated in the most reactive part, i.e. in the arteriolar segment and pressure at the microvascular receptor, P_{rm} , is assumed to equal the mean distending pressure in the microvascular section (P_{dm}).

The instantaneous excitation level, E_{Rm} , of the slowly adapting, myogenic force-sensitive receptor mechanism (index refers to the microvascular section) is assumed to be proportional to the difference between the excitatory current, I_{Em} , and the inhibitory current, I_{Im} , such that

$$E_{Rm} = v_m (I_{Em} - I_{Im}), \quad (22)$$

where v_m is a constant.

The excitatory current, I_{Em} , is assumed to be proportional to the myogenic receptor force, F_{Rm} , giving

$$I_{Em} = g_m F_{Rm}, \quad (23)$$

where g_m is a constant, and the inhibitory current, I_{Im} , is assumed to be a function of a first order process. Thus,

$$\dot{I}_{Im} = (\zeta_m E_{Rm} - I_{Im}) / \tau_{Im}, \quad (24)$$

where ζ_m and τ_{Im} are constants.

No adaptation is assumed in the proximal arterial section but, instead a propagation process is considered. In the model this delay in the excitation in the proximal section, E_{Rp} , is expressed as

$$\dot{E}_{Rp} = (g_p F_{Rp} - E_{Rp}) / \tau_{pp}, \quad (25)$$

where F_{Rp} is the myogenic receptor force; g_p a constant; and τ_{pp} the time constant of the propagation process, which we assumed to be a function of $\dot{E}_{Rp}$. We thus obtain for τ_{pp} :

$$\tau_{pp} = \begin{cases} \tau_{pM} & \text{for } \dot{E}_{Rp} \geq 0 \\ \tau_{pN} & \text{for } \dot{E}_{Rp} < 0 \end{cases} \quad (26)$$

where τ_{pN} and τ_{pM} are constants.

Excitation-contraction coupling

Excitation of the myogenic receptor, E_R , in the proximal as well as the microvascular section is assumed to cause a calcium current, $(I_{Ca})_F$, that is exponentially dependent on the excitation:

$$(I_{Ca})_F = E_R \exp(\gamma E_R), \quad (27)$$

where γ is a constant.

In addition to the force-sensitive calcium influx, a chemically controlled calcium influx, $(I_{Ca})_R$, passing through pharmacological receptor-operated channels is assumed. Thus, the total calcium inflow $(I_{Ca})_T$ will be

$$(I_{Ca})_T = (I_{Ca})_F + (I_{Ca})_R. \quad (28)$$

By assuming that the efflux of calcium is proportional to the level of intracellular activator calcium, Ca^{2+} , this latter quantity will be proportional to the total influx of calcium. Thus,

$$[Ca^{2+}] = \varepsilon (I_{Ca})_T, \quad (29)$$

where ε is a constant.

The Ca^{2+} -force relationship in smooth muscle is described by the following formula:

$$n_{Ca} = \frac{n_M}{1 + \frac{K_F}{[Ca^{2+}]^{n_F}}} \quad (31)$$

where n_{Ca} is a parameter reflecting the stationary relative number of activated cross-bridges; n_M is the saturation value for n_{Ca} ; n_F a constant; and K_F a factor which is assumed to be a function of the interstitial concentration of vasoactive dilator substances (see below).

An assumption made in this model is that the Ca^{2+} -force relationship is the rate-limiting step in the excitation, excitation-contraction coupling. This is expressed as

$$\dot{n}_a = (n_{Ca} - n_D) / \tau_{Ca}, \quad (32)$$

where $\dot{n}_a$ is a parameter reflecting the relative number of activated cross-bridges; and τ_{Ca} the time constant for the activation-deactivation process.

METABOLIC CONTROL

The interstitial concentration of a vasoactive dilator substance, m_i , is assumed to mediate the blood flow dependent metabolic effects suggested in Paper IV:

$$m_i = C_M \frac{m_f}{Q}, \quad (37)$$

where C_M is a constant; m_f the amount of dilator substance produced in the parenchymal cells per unit time; and Q the blood flow.

The reaction time of the metabolic autoregulatory control system is expressed as

$$[\dot{m}_i] = (C_M \frac{m_f}{Q} - [m_i]) / \tau_M, \quad (38)$$

where C_M is a constant as defined above; and τ_M a time constant.

The metabolic factor(s) are assumed to exert their influence in two ways: Firstly, an effect on the excitation-contraction coupling and secondly, an effect on the shortening velocity of the smooth muscle. The former effect is incorporated in the model by letting the metabolic factor (m_1) shift the Ca^{2+} -force relationship Eq. 31 by affecting the apparent dissociation constant K_F . This influence was best described by a power function. Thus,

$$K_F = K_{F0} + Z_F [m_1]^{q_F}, \quad (39)$$

where K_{F0} , Z_F and q_F are constants.

The metabolic effect on the shortening velocity was incorporated by letting m_1 affect the parameter a_v (reflecting v_{max}) in Eq. 13. This influence was also described by a power function. Thus we obtain

$$a_v = \frac{a_{v0}}{1 + Z_v [m_1]^{q_v}}, \quad (40)$$

where a_{v0} , Z_v and q_v are constants.

PARAMETER ESTIMATION

All the parameters included in the model were now to be given proper values. A first step in this procedure was to make use of the current physiological literature. Parameter values obtained in this way are presented in Table I.

A second step was to make use of initial stationary conditions of the differential equations (all derivatives must be zero at rest). This process gives initial values for the state variables or, if they are defined otherwise, another constant parameter in the equation can be determined. The last step in obtaining proper values for the remaining undefined parameters was to assume values and by comparing model predictions to corresponding experimental observations, modify the values of the assumed parameters until satisfying similarity is obtained. Parameters estimated in these ways are presented in Table II.

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